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EXAMINER	
HOWARD, ZACHARY C	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	**Application No.** 10/682,230	**Applicant(s)** LAMB ET AL.	
	Examiner Zachary C. Howard	**Art Unit** 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 September 2007*.
2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.
3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-10 and 12-24* is/are pending in the application.
  4a) Of the above claim(s) *5,7,8,13 and 15-24* is/are withdrawn from consideration.
5)☐ Claim(s) _____ is/are allowed.
6)☒ Claim(s) *1,2,4,6,9,10,12 and 14* is/are rejected.
7)☐ Claim(s) _____ is/are objected to.
8)☒ Claim(s) *1,2,4-10 and 12-24* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.
10)☒ The drawing(s) filed on *04 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.
  Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
  Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
  a)☒ All b)☐ Some * c)☐ None of:
    1.☐ Certified copies of the priority documents have been received.
    2.☐ Certified copies of the priority documents have been received in Application No. _____.
    3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
  * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
  Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413)
  Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 9/10/07 has been entered in full. Claims 1 and 9 are amended. Claims 3 and 11 are canceled.

This application contains claims 17-24 drawn to an invention nonelected with traverse in Applicants' response filed 7/26/06. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01.

Claims 5, 7, 8, 13, 15 and 16 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

Claims 1, 2, 4, 6, 9, 10, 12 and 14 are under consideration, in so far as they read on the elected species of (1) "Sonic Hedgehog signaling pathway" and (2) "upregulator".

Oath/Declaration

As stated in MPEP 602.02, "[w]here neither the original oath or declaration, nor the substitute oath or declaration is complete in itself, but each oath or declaration names all of the inventors and the two taken together give all the required data, no further oath or declaration is needed." As set forth in the 3/9/07 Office Action, the 3/4/04 Declaration was properly executed by each Applicant except Jonathan Robert Lamb. On 9/10/07, Applicants filed a declaration properly executed by Jonathan Robert Lamb. Therefore, in accordance with MPEP 602.02 the combination of the two declarations is sufficient to complete a declaration that meets the requirements of 37 CFR 1.67(a).

Withdrawn Objections and/or Rejections

The objections to the specification at pg 4 of the 3/9/07 Office Action are *withdrawn* in view of Applicants' amendments to the specification.

All rejections of claims 3 and 11 are moot in view of Applicants' cancellation of these claims.

Maintained Objections and/or Rejections

Claim Rejections - 35 USC § 112, 1st paragraph, enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4, 6, 9, 10, 12 and 14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of upregulating T-cell activation, or proliferation, comprising administering to *in vitro* T-cells an anti-CD3 antibody, anti-CD28 antibody and the 19kDa N-terminal autoproteolytic Sonic hedgehog (Shh) peptide, does not reasonably provide enablement for a method of modulating T-cell activation or proliferation comprising administering to T-cells a modulator of a Hedgehog signaling pathway. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This rejection was set forth at pg 4-9 of the 3/9/07 Office Action.

Applicants' arguments (9/10/07; pg 7-8) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response, Applicants first argue that, "in a treatment setting, CD3 and CD28 would be activated as a part of the ongoing immune responses, as known in the art"; in support, Applicants point to Bromley et al (2001). Applicants argue that "anti-CD3 and anti-CD28 antibodies were added to improve the validity of the *in vitro* model, not as a part of the treatment."

These arguments, and Bromley et al (2001), have been fully considered and are found persuasive in part. It is true that T-cell activation via the cell-surface molecules CD3 and CD28 is part of ongoing immune responses, and thus general activation of T-cells in response to antigens does not require administration of anti-CD3 or anti-CD28 antibodies. However, the claims are not limited to an *in vivo* treatment setting; specifically, the introduction of the term "administering" to the amended claims does not limit the claims to administering to T-cells as opposed to administering to isolated T-cells (e.g., harvested or cultured T-cells). Therefore, with respect to isolated T-cells, it is maintained that specification does not provide any guidance on how to use the Shh protein as a modulator of T-cell activation in the absence of anti-CD3 and anti-CD28 antibodies, and it would require undue experimentation to determine how to use the Shh protein in this manner.

With respect to the scope of the "upregulator" encompassed by the claims, Applicants argue that the amended claims are now limited to "upregulators" of the Hedgehog signaling pathway (i.e., "upregulators" of targets pathways have been removed from the claims). Applicants further argue that, "the specification provides numerous examples of various upregulators that are encompassed by the claimed invention"; in support, Applicants point to page 18, line 28 to page 22, line 18. Applicants further argue that the specification provides "assays that can be used to confirm activity of any particular upregulator"; in support, Applicants point to page 22 line 19 to page 23, line 17.

These arguments have been fully considered but are not found persuasive. The specification from page 18, line 28 to page 22, line 18 includes general teachings regarding "compounds that increase (agonise) Hedgehog signaling" (pg 19, lines 5-6) but provides extremely limited (as compared to the breadth of the genus of potential upregulators) guidance regarding specific upregulators that can be used in the claimed method. In this section, the only specific upregulators that are disclosed are "[e]xamples of such agonists include the positive regulators of HH signaling Smo and Gli" (pg 20, lines 24-25). However, as set forth previously, these compounds are significantly different than Shh in function; specifically, while Shh is a secreted protein, the Smo receptor is membrane-bound and Gli is an cytoplasmic protein. There is no working example of a method wherein T-cells are contacted with either the Smo receptor or the Gli protein that results in T-cell activation or proliferation, and it would require undue experimentation to determine how a membrane-bound or intracellular protein could be administered to function as an upregulator of Hedgehog signaling.

In order the practice the claimed method of modulation with a genus of "upregulators", the skilled artisan must be identify said upregulators without undue experimentation. The disclosure of an assay to identify upregulators does not allow the skilled artisan to identify upregulators that will function in the claimed method. As set forth previously, the claims encompass methods of upregulating T-cell activation, or proliferation, with upregulators of a Sonic Hedgehog (Shh) signaling pathway other than the biologically active 19kDa N-terminal autoproteolytic Shh peptide. The claims encompass a vast genus of potential upregulators including compounds such as small molecules, proteins, nucleic acids, and more. However, the specification provides little guidance as to the nature of specific upregulators of Shh signaling pathway that can be used able to modulate T-cell activation or proliferation. The specification provides a single working example of an upregulator (19kDa N-terminal autoproteolytic Shh peptide) that works in the claimed method when practiced *in vitro*. The specification further teaches that a large variety of small molecules that are "modulators" of the hedgehog signaling pathway (pages 38-51). However, there is no guidance provided by the specification as to which of these small molecules are upregulators and which are inhibitors. There is no guidance regarding the mechanism of interaction of these molecules with a Hedgehog pathway. Furthermore, there is no working example of a method wherein one of these putative Hedgehog signaling modulators is used specifically for T-cell activation or proliferation. The specification merely demonstrates that T-cells can be contacted with the Shh peptide to activate the T-cells, and then suggests that any agonist of a Shh signaling pathway can be used in a similar manner. In view of the breadth of the genus of upregulators encompassed by the claims and the minimal guidance regarding specific upregulators in said genus that will work to activate or proliferate T-cells, the claims lack enablement for the full scope of the claims. The specification merely invites the skilled artisan to screen compounds to identify upregulators of a Shh signaling pathway that can upregulate T-cell activation or proliferation.

Applicants further argue that, "the specification provides substantial guidance for practicing for practicing the present invention *in vivo*" (pg 8). Applicants argue that the specification amply describes the form, route and dosage for administration of a modulator; in support, Applicants point to teachings beginning pages 80 and 83.

These arguments have been fully considered but are not found persuasive. The teachings on pages 80 and 83 of the specification provide lists potential routes of administration and dosages of modulators. However, as set forth in the previous Office Action, the specification does not provide any working examples of modulation of *in vivo* T-cell activation or proliferation with modulators. Furthermore, it is maintained that the relevant art supports that the skilled artisan could not predict whether or not administration of Shh or a modulator of a Shh signaling pathway would result in an increase, a decrease or no effect on T-cell activation or proliferation. Outram et al (2000) teaches that Shh inhibits thymocyte development in the DN (double negative) CD4- CD8- stage (Outram et al, 2000. Immunity. 13: 187-197; cited previously). Thus, Sonic hedgehog signaling is involved in other *in vivo* processes related to thymocytes that may interfere with T-cell activation or proliferation. In view of this unpredictability, the skilled artisan would need to engage in undue experimentation to determine whether or not Shh, or another modulator of a Shh signaling pathway or another target pathway, could be used for any form of treatment. This undue experimentation would need to be completed prior to any routine determination of optimal methods of administration or dosages.

It is noted that the following portion of the enablement rejection is moot in view of Applicants' amendments to the claims: part (3) at pg 7-8 is moot in view of Applicants' amendments that delete the recitation of "or a modulator of a pathway which is a target of the Hedgehog signaling pathway".

Claim Rejections - 35 USC § 112, 1st paragraph, written description

Claims 1, 2, 4, 6, 9, 10, 12 and 14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection was set forth at pg 10-12 of the 3/9/07 Office Action.

Applicants' arguments (9/10/07; pg 8-9) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response, Applicants argue that the amended claims are now limited to "upregulators" of the Hedgehog signaling pathway (i.e., "upregulators" of targets pathways have been removed from the claims). Applicants further argue that, "the specification describes a representative number of species of upregulators of a Hedgehog signaling pathway; in support, Applicants point to page 18, line 28 to page 22, line 18.

These arguments have been fully considered but are not found persuasive. The specification from page 18, line 28 to page 22, line 18 includes general teachings regarding "compounds that increase (agonise) Hedgehog signaling" (pg 19, lines 5-6) but provides extremely limited (as compared to the breadth of the genus of potential upregulators) description of the structure of specific upregulators. In this section, the only specific upregulators that are disclosed are "[e]xamples of such agonists include the positive regulators of HH signaling Smo and Gli" (pg 20, lines 24-25). However, as set forth previously, these compounds are significantly different than Shh in function; specifically, while Shh is a secreted protein, the Smo receptor is membrane-bound and Gli is an cytoplasmic protein. There is no description of a method wherein T-cells are contacted with the Smo receptor or the Gli protein that results in T-cell activation or proliferation. As such, the skilled artisan would not consider these compounds to represent described compounds that could be used in the claimed method as upregulators.

Applicants further argue that "structural details" regarding upregulators of Shh signaling are not need in the claimed methods because "a large number of modulators that can upregulate Shh signalling are known in the art, including the proteins and non-protein organic molecules described in the specification" (pg 8).

These arguments have been fully considered but are not found persuasive. As set forth previously, the genus of potential upregulators is highly variant because an essentially unlimited number of structural differences are permitted between genus members. Potential genus members include chemical entities, pharmaceutical compositions, proteins, peptides, non-peptide compounds, animal tissue extracts, nucleic acids, antisense molecules, peptidomimetic, transformed cells, radiation, antibodies, antibody fragments, cyclic peptides, agonists, antagonists, inhibitors, enhancers, vegetable extracts, cell extracts, synthetic agents, biologically derived substances as well as proteinaceous substances, known, and unknown compounds. At the time of filing of the instant application (April 9th, 2002), the relevant art did not appreciate upregulators of Shh signaling that were commensurate in scope with the breadth of the "upregulator" genus encompassed by the claims. The specification describes the Sonic hedgehog protein as an upregulator of the pathway that can be used in the claimed invention. Pages 38-51 provide a large variety of small molecules that are described as "modulators" of the hedgehog signaling pathway. However, there is no description of which of these small molecules are upregulators and which are inhibitors. There is no description of the mechanism of interaction of these molecules with the hedgehog pathway. Most importantly, there is no description of a method wherein one of these molecules is used for T-cell activation or proliferation. Therefore, for the reasons set forth in the previous Office Action, it is maintained that only a method of modulating T-cell activation or proliferation comprising contacting T-cells with the 19kDa N-terminal autoproteolytic Sonic hedgehog peptide, but not the full breadth of the claims meets the written description provision of 35 U.S.C. §112, first paragraph.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4, 6, 9, 10, 12 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Van Gool et al, 1993 (The Journal of Immunology. 150(8): 3254-3263; cited previously). This rejection was set forth at pg 13-14 of the 3/9/07 Office Action.

Applicants' arguments (9/10/07; pg 9) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response, Applicants argue that amended claims require "administering a modulator of a Hedgehog signaling pathway to T-cells", and that Van Gool does not teach a method comprising "administering". Applicants argue that the claimed method is "clearly different" because Van Gool only teaches that, "T-cells ... were merely placed into culture plates coated with anti-CD3 and anti-CD28.

Applicants' arguments have been fully considered but are not found persuasive. The instant specification does not provide a limiting definition of the term "administering". The definition of the term "administer" includes "to make application; give" (see the first page of the Dictionary.com definition of "administer"; printed on 11/15/07). In the teachings of Van Gool, the T-cells were cultured on plates coated with anti-CD3 antibody and in the presence of 200 ng/ml of anti-CD28. This teaching meets the definition of administer with respect "to make application"; the methodology taught by Van Gool results in application of the anti-CD3 antibody and the anti-CD28 antibody to T-cells. As the term "administering" encompasses in vitro application of modulators to T-cells, it is maintained that the teachings of Van Gool anticipate the claims for the reasons set forth in the previous Office Action.

Claims 1, 2, 4, 6, 9, 10, 12 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Outram et al, 2000 (Immunity. 13: 187-197; cited previously). This rejection was set forth at pg 14-15 of the 3/9/07 Office Action.

Applicants' arguments (9/10/07; pg 9) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response, Applicants argue that Outram "does not teach each and every element of the claimed invention, as Outlam [sic] relates to thymocyte development, namely cellular differentiation, while the present invention claims a method of modulating T-cell activation." In support, Applicants point to the Abstract of Outram as teaching, "our data suggests termination of Hh signaling is necessary for differentiation". Applicants argue that the instant specification discloses upregulation of Shh signaling.

Applicants' arguments have been fully considered but are not found persuasive. As set forth in the previous Office Action at pg 14, the recitation of "modulating T-cell activation" or "modulating T-cell proliferation" in the preamble of the claims from the instant application is interpreted as an intended use and bears no accorded patentable weight to distinguish a claimed product over one from the prior art. Furthermore, the specification provides no limiting definition of "T-cell activation" or "T-cell proliferation". Therefore, the claims have been interpreted as encompassing any method of "activating" a cellular process in T-cells comprising contacting T-cells with a modulator of Hedgehog signaling.

Outram teaches that a "neutralizing antibody against Shh accelerates thymocyte development in thymus explants" (pg 188). Outram teaches "culturing thymocytes with the anti-Hh neutralizing antibody 5E1" and "neutralization of Shh greatly increased thymocyte differentiation over this 3 day time period" and "there was a 2- to 3.5- fold increase in the number of thymocytes recovered from the cultures containing the neutralizing antibody" (pg 188-189). Therefore, Outram teaches a method of comprising contacting T-cells with a modulator of Hedgehog signaling and anticipates instant claims 1, 2, 4, 6, 9, 10, 12 and 14.

Claims 6 and 14 each encompass an upregulator that is an “antibody”. Therefore, the method taught by Outram comprising contacting T-cells with anti-Shh antibody also anticipates each of claims 6 and 14.

Claims 1, 2, 4, 6, 9, 10, 12 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Stewart et al, December 2000 (Immunology. 101(Supplement 1): pg 14; cited previously). The publication date of Stewart (December 2000) is more than one year prior to the earliest U.S. filing date to which the instant application claims priority (4/9/02). cited previously). This rejection was set forth at pg 15 of the 3/9/07 Office Action.

Applicants' arguments (9/10/07; pg 9-10) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response, Applicants argue that “[a]s was true of Outlam [sic], Stewart also does not teach each and every element of the present invention because Stewart refers only to T-cell proliferation, and not activation, as claimed” (pg 10).

Applicants' arguments have been fully considered but are not found persuasive. First, claim 9 specifically recites “[a] method of modulating T-cell proliferation”. Therefore, Applicants' arguments are not persuasive in this regard because claims 9, 10, 12 and 14 each encompass T-cell proliferation, which Applicants acknowledge is taught by Stewart. Furthermore, as set forth in the previous Office Action, the teachings of Stewart are also directed to T-cell activation. Specifically, Stewart teaches, “[t]he addition of Shh enhances the proliferative response of both CD4+ and CD8+ cells following stimulation with αCD3 and αCD28” (pg 14), and stimulation with anti-CD3 and anti-CD28 antibodies inherently causes T-cell activation. Therefore, Applicants' arguments are not persuasive with respect to claims 1, 2, 4 and 6. It is maintained that Stewart anticipates the instant claims for the reasons set forth previously.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646